REMARKS

Claims 48-50, 53-62, 65-68, 70-73 and 76-79 are pending in this application. Claims 51-52, 63-64, 69 and 74-75 have been cancelled from the application without prejudice in this reply. In addition, claims 48, 50, 53-55, 58-59, 65 and 68 have been amended and new claims 77-79 have been added to the application in this Reply. Finally, the application Abstract and the priority claim have been amended in this Reply. No new matter has been added to the application specification or claims by any of these amendments.

A marked up version of the application claims are attached to this Reply as Appendix A. A clean version of all pending application claims are attached to this Reply as Appendix B.

The Examiner's specification and claim objections and rejections are traversed and/or overcome as set forth below:

Rejection Of Claims 48-49 and 68-72 over Regnier under 35 U.S.C. 102(b)

The Examiner has rejected claims 48-49 and 68-72 as being anticipated by Regnier. Applicants respectfully traverse the rejection.

A rejection under 35 U.S.C. 102(b) is only appropriate when every element in the rejected claim exists in a single prior art reference. None of the compounds disclosed and claimed by Regnier are within the scope of the claims of the present application. The compounds disclosed and claimed by Regnier require a heterocycle (designated as A) to be linked to a bicyclic (or tricyclic) unit attached to the pyrimidine ring of the purine (thus forming a tricyclic or tetracyclic structure). Note that Applicants' claims do not permit such a configuration because in the compounds of the present invention as claimed:

1) R_1 is attached to the pyrimidine ring by an -NH- or -SO_2- group. The NH group is not permitted to be incorporated into a ring structure (a heterocycle) as required by Regnier; and

2) R_3 cannot be a substituted heterocycle, as required by Regnier.

Applicants respectfully submit that the rejection of claims 48-49 and 68-72 as being anticipated by Regnier is incorrect, and should be withdrawn.

Rejection Of Claims 48-53, 56-57, 61, 64 and 68-76 over WO 97/16452 under 35 U.S.C. 102(a)

The Examiner has rejected claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(a) as being anticipated by WO 97/16452. Applicants respectfully traverse the rejection.

The publication date of WO 97/16452 is shown on the face of the document as May 9, 1997, which is after the filing date of the parent application of the present application (US 5,866,702, filed August 2, 1996). Thus if WO 97/16452 is available as prior art at all in the U.S., it would only be with respect to material added to the present application that is not within the scope of the parent.

It should be noted that there is very little overlap between WO 97/16452 and the present application. Note that the R_4 and R_5 of WO 97/16452 (which are substituents of the 2-amino group) are defined to include phenylamino, and alkylamino - these moieties are not possible substituents in the present invention (phenylamino and alkylamino substitutions provide hydrazine derivatives, not amino derivatives). The other disclosed definitions of R_4 and R_5 in WO 97/16452 include hydrogen, amino, lower alkoxy, phenoxy, acyl, and a substituted aliphatic radical. All of these definitions are clearly within the scope of the US 5,866,702 parent (see the definitions related to -NR_4R_5 in '702).

Thus, WO 97/16452 discloses either material that is clearly within the scope of the parent US 5,866,702 parent, or discloses material that is not within the scope of the parent or the present application. Accordingly, Applicants respectfully submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(a) as being anticipated by WO 97/16452 is in error, and should be withdrawn.

Rejection Of Claims 48-53, 56-57, 61, 64 and 68-76 over Norman under 35 U.S.C. 102(b)

The Examiner has rejected claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(b) as being anticipated by Norman. Applicants respectfully traverse the rejection.

The Examiner points to the species named in Norman at page 7431 as not being subject to the proviso of claim 1. This species is disclosed as 2-((2-hydroxyethyl)amino)-6-((4-methoxybenzyl)amino)-9-(isopropylamino). This is clearly improperly named, but presuming that the intention was to name it as a purine derivative, Applicants point out that this exact compound is disclosed in the US 5,866,702 parent - see page 3 of the Certificate of Correction, row 9, in which R_1-X is 4-methoxybenzylamino, R_2 is isopropyl, and R_3 is ethanolamino.

Norman was not available to the public until after the filing date of the parent application (The Journal that includes the Norman article was published on August 7, 1996, as confirmed with The Journal of the American Chemical Society). Thus, if Norman is available as prior art in the U.S. at all, it would only be with respect to material added to the present application that is not within the scope of the parent. The disclosure of Norman is clearly within the scope of '702. Accordingly, Applicants respectfully submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(b) as being anticipated by Norman is in error, and should be withdrawn.

Rejection Of Claims 48-49, 51, 56 and 76 over McAfee (US 5,117,830) under 35 U.S.C. 102(b)

The Examiner has rejected claims 48-49, 51, 56 and 76 over McAfee (US 5,117,830) under 35 USC 102(b), alleging that the species disclosed at column 4 of McAfee, species 4, anticipates the claims of the present application.

The species 4 is named as N^6-1-(2-thienyl)-2-butyl-9-MA, which (although not explicitly explained) is presumably intended to be N^6-1-(2-thienyl)-2-butyl-9-methyladenine. Applicants respectfully submit that even if it were true that this species anticipated Applicants' claims, Applicants have amended the claims in order to expedite prosecution of the application so that this species is no longer within the scope of the claims (when R_1' is optionally substituted alkyl, the optional alkyl substitution is not heteroaryl).

Accordingly, Applicants respectfully submit that the rejection of claims 48-49, 51, 56 and 76 over McAfee (US 5,117,830) under 35 USC 102(b) is moot. Applicants reserve the right to pursue the canceled claims in a continuing application.

Rejection Of Claims 48-49, 51, and 56 over Seyama under 35 USC 102(b)

The Examiner has rejected Claims 48-49, 51, and 56 under 35 U.S.C.§ 102(b) as being anticipated by Seyama. Applicants respectfully traverse the rejection.

The Examiner points to compound 39 (sic, presumably compound 35) of Seyama as being within the scope of Applicants' claims, because it "corresponds to R_3 = substituted heteroaralkyl". Although not necessarily agreeing that the Seyama substitution could be

considered as a heteroaralkyl as defined in the present application, Applicants have amended claim 48 such that R_3 cannot be "heteroaralkyl", and thus the rejection is now moot.

Applicants submit that the rejection of claims 48-49, 51 and 56 under 35 U.S.C.§ 102(b) as being anticipated by Seyama should be withdrawn. Applicants reserve the right to pursue the canceled claims in a continuing application.

Rejection Of Claims 48-53, 56-57, 61. 64, and 68-76 over Vesely under 35 USC 103(a)

The Examiner has rejected claims 48-53, 56-57, 61. 64, and 68-76 over Vesely under 35 USC 103(a). Although not necessarily agreeing that any claims of the present application are rendered obvious by Vesely, Applicants have amended claim 1 with a proviso that when R_1 is benzyl or phenylethyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, R_2 is not [lower alkyl of C_{1-4}] methyl or ethyl. Thus the rejection is now moot.

Applicants submit that the rejection of claims 48-53, 56-57, 61. 64, and 68-76 over Vesely under 35 USC 103(a) should be withdrawn. Applicants reserve the right to pursue the canceled claims in a continuing application.

Rejection Of Claims 48-53, 56-57, 61. 64, and 68-76 over De Azvedo under 35 USC 103(a)

The Examiner has rejected Claims 48-53, 56-57, 61. 64, and 68-76 over De Azvedo under 35 USC 103(a).

Applicants have amended claim 1 with a proviso that when R_1 is benzyl or phenylethyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by

hydroxy or amino, R_2 is not [lower alkyl of C_{1-4}] methyl or ethyl. Thus even if De Azvedo is prior art to the present application, which it is not, the rejection is now moot.

Applicants reserve the right to pursue the canceled claims in a continuing application.

Rejection Of Claims 48-53, 56-57, 61. 64, and 68-76 over U.S. 6,316,456 under 35 USC 103(a)

The Examiner has rejected claims 48-53, 56-57, 61. 64, and 68-76 over U.S. 6,316,456 under 35 USC 103(a). Applicants respectfully traverse the rejection.

U.S. Patent No. 6,316,456 is derived via §371from a PCT application, which was filed on November 29, 1996, published on June 12, 1997. Thus, it was published after the filing date of US Patent 5,866,702, filed August 2, 1996), which is the parent of the present application.

Thus, if '456 is available as prior art in the U.S. at all, it would only be with respect to material added to the present application that is not within the scope of the parent. Thus, U.S. Patent No. 6,316,456 is not available as prior art to the present application, and the rejection is moot.

The 35 U.S.C. §112. Second Paragraph Rejections

The Examiner rejected Claims 48-76 under 35 U.S.C. §112, second paragraph on several different grounds. The Examiner's 112, second paragraph rejections are overcome or traversed in the numbered paragraphs below.

1. The examiner asks as to the definition of optional substitutions of R_1'. R_1' is defined as lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl,

cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, aralkyl, hetaryl, substituted hetaryl, and heteroalkyl.

The Examiner's attention is drawn to the specification on page 11, lines 15-20, where support for the term substituted lower alkyl is found. On page 14, lines 13-16, the definition of substituted cycloalkyl is found. On page 14, lines 19-22, the definition of substituted cycloheteroalkyl is found. On page 13, lines 2-5, the definition of substituted aryl is found. On page 13, lines 20-23, the definition of aralkyl and the appropriate optional substitutions are found. On page 13, lines 55-18, the definition of substituted heteroaryl (or hetaryl) is found.

Claims are to be read in light of the disclosure of the specification. Accordingly, all optional substitutions recited in the definition of R_1' are found in the specification.

2. The claim definitions as amended no longer recite "alkylthiol" - thus the rejection is now moot.

3. The Examiner alleges that the potential substituents listed in claim 63 for R_3 are "garbled". Although Applicants do not agree with this characterization, in the interests of advancing the application to allowance, Applicants have canceled claims to (RS)-leucinol, L-histidinol, and (R)-2-amino-3-phenyl-1-propanol. Applicants reserve the right to pursue such claims in a continuing application.

4. The Examiner has objected to the use of the word "acetylene" in the claims. However, the claim definitions as amended no longer recite "acetylene", or the original replacement "ethynyl" - thus the rejection is now moot..

5. The Examiner alleges that a number of the disorders of claim 71 are not cell proliferative disorders. Applicants respectfully disagree.

As discussed in detail previously, all of the disease states listed are known in the art to be treatable by a CDK-2 inhibitor. Such disease states are primarily cell proliferative disorders (cancer, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis, diabetes, and graft versus host disease), or have cell proliferation as a part of the sequelae of the disease (gout, diabetes). Pathological cell proliferation may also be the result of wounding, including surgical wounding, as in the case of restenosis.

In any event, in order to expedite allowance of the claims, Applicants have amended claim 71 to include disease states that have been previously allowed in similar patents. See, for example, U.S. Patent Nos. 6,498,163 and 6,503,914, in which similar language is employed (see claim 11 of the '163 patent and claim 11 of the '914 patent. Applicants respectfully submit that one of ordinary skill in the art would understand that a CDK-2 inhibitor would have the utilities claimed in claim 71,

6. The extraneous semicolon after "or" has been removed from claim 48, as suggested by the Examiner.

7. The definition of R_3 has been amended in order to clearly set forth the claimed moieties and the optional substitutions possible for such moieties.

Rejection Of Claim 68 under 35 USC 112, Second Paragraph

The Examiner has rejected claim 68 under 35 USC 112, second paragraph. Applicants respectfully traverse the rejection.

A. The Examiner alleges that the claim potentially could cover all disease states. This is incorrect. The claim covers any disease state that is treatable by a CDK-2 inhibitor. Applicants have demonstrated that the compounds of the invention are CDK-2 inhibitors and/or IκB-α inhibitors, and thus the compounds are useful for treating disease states that are capable of modulation by a CDK-2 inhibitor or IκB-α inhibitor.

In any event, in order to expedite prosecution of this application, Applicants have amended claim 68 to recite "A method of inhibiting a cell cycle kinase, comprising administering to a mammal in need thereof a therapeutically effective dose of a compound of claim 48". This mode of claiming a method of use of compounds is believed to be acceptable practice in the U.S. Patent Office - see, for example, U.S. Patent Nos. 6,498,163 and 6,503,914, in which similar language is employed (see claim 11 of the '163 patent and claim 11 of the '914 patent.

Please also note that the issued claims of the '163 patent include claims to a method of treating proliferative diseases selected from the group consisting of cancer, psoriasis, vascular smooth muscle proliferation associated with a disorder selected from the group consisting of athersclerosis, postsurgical vascular stenosis, and restenosis (claim 26). Such claims were allowed on the basis of in-vitro testing that demonstrated that the compounds of the invention were inhibitors of the CDK kinases. There was no in-vivo testing.

Please also note that similar claims were obtained in the '914 patent, again on the basis of in-vitro determinations of activity.

In light of the issued claims of the two patents cited above (there are many more if the Examiner would like further comparison), it is evidently normal practice to obtain claims to various disease states based upon in-vitro determinations of appropriate activity of novel compounds. The Examiner states, "It is quite common for pharmaceuticals to work only with some people, not all". However, this is not the standard for a rejection under 35 USC 112, second paragraph. If it were, there would be no pharmaceutical compound patents issued, as such detail is rarely if ever known at the time of filing a patent application. In any event, the question of whether the claimed compounds are effective in humans is within the province of the FDA, not the U.S. Patent Office.

The asserted claims are credible in light of what is known in the art with respect to CDK-2 inhibitors. Compounds similar to those of the present invention have similar properties, and one of ordinary skill would find it credible that compounds that are demonstrated to be CDK-2 inhibitors are capable of treating the claimed disease states. A patent application is not required to provide safety or efficacy data to support claims to treatment of a disease. Applicants respectfully submit the rejection of claim 68 under 35 USC 112, second paragraph should be withdrawn.

Applicants reserve the right to pursue the canceled claims in a continuing application.

B. The Examiner alleges that replacement of "thio" with "mercapto" is new matter. Although not agreeing with this statement, Applicants have amended the claims to remove the term "mercapto" and or "thio". Applicants reserve the right to pursue such claims in a continuing application.

C and D. Applicants have canceled the term "substituted aralkyl" from the definitions of R_1' and R_2.

E. The Examiner states that the three provisos lack description, citing Ex Part Grasselli (231 USPQ 393) for the proposition that a negative limitation requires description in the specification. Applications respectfully traverse the rejection.

The provisos are simply present to eliminate compounds that may be within the prior art from the scope of the claims (for example, the known compound olomoucine). The issue is not that there is any uncertainty introduced by such provisos -the species removed from the claims by proviso are clearly useful for their stated utility. The Board stated, relative to the issue in Grasselli:

> It might be added that that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts. Id, 399.

Equally clearly, this is not the situation in the present application. There are no "new concepts" introduced by the three provisos - they do not imply the inclusion of any other "elements".

The Examiner's rejection can be overcome by removing the provisos from claim 1. If this were done, then the result of their removal could be a first Office action rejecting the claim under 35 U.S.C. 102. Such a rejection could be then be overcome by excluding such compounds from claim 1 by proviso. Presumably the Examiner is not suggesting that Applicants have no right to do so in response to such a rejection? But the result is exactly the same as including the three provisos in the instant claims.

Applicants respectfully submit that the rejection under 35 U.S.C. 112, First Paragraph, should be withdrawn.

F. The claims have been amended in order to include the provisos present in the parent case, U.S. Patent 5,866,702. Thus, the claims are no broader than originally filed.

G. The term "alkoxy" has been replaced by the term "lower alkoxy" with respect to the optional substitutions of R_2.

I. The term "heteroarylalkyl" has been removed from claim 1 - thus the issue of whether the substituents are included in the original specification is now moot.

K. Although not agreeing with the Examiner's ground of rejection, Applicants have amended Claim 68 to recite "A method of inhibiting a cell cycle kinase characterized as CDK2", thus rendering the rejection moot.

M. Although not agreeing with the Examiner's characterization of claim 70 as lacking description in the specification, Applicants have amended the claim to include the language suggested by the Examiner (treating a proliferative disease where pathogenesis involves abnormal cell proliferation). Thus, the rejection is now moot.

N. The choice of substituted heteroarylalkyl for R_2 and R_3 has been canceled, thus rendering this rejection moot.

The Examiner has also rejected Claim 70 as being too broad. As Claim 70 is dependent upon Claim 68, and Claim 68 has been amended in accordance with the Examiner's suggested language, the rejection is now moot.

The Examiner has rejected Claims 74 and 75 as not enabled. Although not necessarily agreeing with the Examiner's ground of rejection, in order to expedite prosecution Applicants have canceled Claims 74 and 75. Applicants reserve the right to pursue such claims in a continuing application.

The Examiner also stated that "The compounds are disclosed to be CDK-2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue

experimentation, treat such difficult disorders with such compounds". Applicants respectfully traverse the rejection.

The quantity of experimentation needed to make or use the invention is related to the content of the disclosure and to what is known in the relevant art.

> A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification.

Northern Telecom, Inc.. v. Datapoint Corp., 15 U.S.P.Q. 1321, 1329 (Fed. Cir. 1990) (see also In re Gay, 135 USPQ at 316, Atlas Powder Co. v. E.I. Du Pont De Nemours and Co., 224 USPQ 409 (Fed. Cir. 1984).

Applicants believe that a person skilled in the art would not need undue experimentation to either prepare or use the claimed compounds. They would understand that CDK-2 inhibitors are useful in the disease states claimed, based upon knowledge freely available in the art. For example, as mentioned above, there are many issued patents that claim novel CDK-2 inhibitors and disclose that they are useful for the utilities claimed in the instant application - see, for example, U.S. Patent Nos. 6,498,163 and 6,503,914.

The Examiner points to several articles (Glaub, Vesely, etc.) for the proposition that references of record do not support the concept that CDK-2 inhibitors are useful for the claimed disease states. Even supposing that this were true (which it is not), the articles cited by the Examiner are from 1994 and 1995 - much progress has been made in this area since then, as evidenced by Applicants invention, and the inventions of numerous patent holders.

The Examiner also states that Applicants' compounds are shown to be (in some instances) less active than olomoucine, and that, as olomoucine is not potent enough to be

effective, therefore the compounds of Applicants' invention are not effective. Applicants submit that this statement is incorrect as a matter of scientific fact and of patent law.

1) Olomoucine has not been shown to be ineffective. In an abstract of a review entitled "Synthetic Cyclin Dependent Kinase Inhibitors: New Generation of Potent Anti-cancer Drugs" a reference to olomoucine states that "its unique mechanism of action and potent anticancer activity under both in-vitro and in-vivo conditions provide a unique tool to inhibit tumor cell proliferation, and to selectively induce aptosis?? in neoplastic tissues". (Abstracted from Advances in Experimental Medicine and Biology (1999), 457).

If the Examiner means to say that olomoucine has not been approved as a marketable product, that is correct. However, such a statement is not synonymous with the proposition that olomoucine is ineffective for its stated purpose.

2) Even if olomoucine was ineffective, the fact that some of the compounds of Applicants' invention show less activity in-vitro than olomoucine is irrelevant. Applicants clearly demonstrate that the compounds of the invention are CDK-2 inhibitors, and CDK-2 inhibitors are well known to possess the claimed utilities. As the court said with respect to research involving prostaglandins:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

In re Bundy, 209 USPQ 48, 51 (CCPA 1981)

The compounds of the present invention are novel compounds that possess significant therapeutic utility. There is no requirement that Applicants delay filing a patent application in order to carry out testing of the compound.

Additionally,

> As we said in Fouche, there is no requirement in §112 that all of the claimed compounds have the same degree of utility. Some antihypertensive activity coupled with knowledge as to the employment of this activity is all that is necessary to satisfy the how-to-use requirement.

In re Gardner, 177 USPQ 396, (CCPA 1973)

> While specific methods of use.....for each and every species covered by the claims have not been demonstrated as pointed out by the examiner, a disclosure of that extent is not required by statute. As stated by the court in In re Grimme et al., 57 CCPA 785, 274 F.2d 949, 1960 C.D. 123, 754 O.G. 6, 124 USPQ 499, 502:
>
> > "It is manifestly impractible for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it"

Ex parte Schundehutte and Trautner, 184 USPQ 697, 699 (POBA 1974)

Applicants respectfully submit that the present disclosure is sufficient to teach those skilled in the art what the invention is, and how to use it. The rejection should be withdrawn.

Double Patenting

Claims 1-2, 8, 10, 14-16, 18, 20, 44-48 are rejected for obviousness double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,866,702. When an indication is received of allowability of the present claims, Applicants will provide an appropriately drafted Terminal Disclaimer.

Parentage

As requested by the Examiner, the statement regarding the parentage of the application has been amended. The Applicant's wish to point out, however, that contrary to the Examiner's assertion, the parent of present application is not a continuation-in-part of PCT/US97/13386 filed 8/1/97. The parent application (serial no. 09/230,829) is identical in scope to PCT/US97/13386. It is PCT/US97/13386 that includes some material not found in the earliest priority application serial no. 08/692012, filed on August 2, 1996.

Abstract Amendment

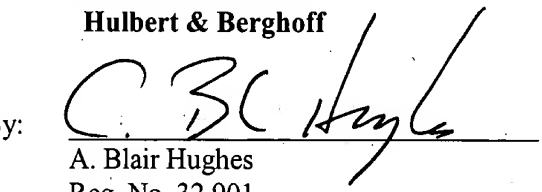
The Abstract has been changed to what is considered to be an acceptable format.

CONCLUSION

The amendments and/or statements in favor of patentability presented above are believed to render all pending application claims allowable. Favorable reconsideration and allowance of all pending application claims is, therefore, courteously solicited.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: March 7, 2003 By: 

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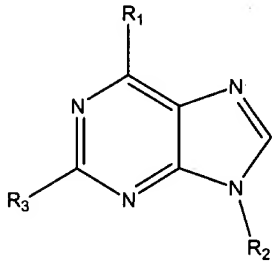
APPENDIX A

Marked Up Copy of the Claims Pursuant To 37 CFR 1.121

IN THE CLAIMS:

48. (twice amended) A compound having the formula:



wherein:

R_1 is -X-R_1'; in which R_1' is lower alkyl, substituted lower alkyl, [cycloheteroalkyl, substituted cycloheteroalkyl], aryl, substituted aryl, [aralkyl, substituted aralkyl, hetaryl, substituted hetaryl, and heteroalkyl] or a heterocycle, and X is -NH- or -SO_2-;

R_2 is lower alkyl optionally substituted with one, two or three groups selected from hydroxy, lower alkoxy, and halogen[, mercapto, alkylthio, amino, amido, carboxy, cyano, aryloxy, alkenyl, alkynyl, or acyl;

aryl, heteroaryl, arylalkyl or heteroarylalkyl where the ring portion of each is optionally substituted with one, two or three groups selected from lower alkyl, alkoxy, halogen, mercapto, alkylthio, ethynyl, amino, amido, carboxy, hydroxy, aryl, aryloxy, heteroaryl, nitro, or cyano;

cycloalkyl optionally substituted with one, two or three groups selected from lower alkyl, alkoxy, halogen, thiol, ethynyl, alkylthio, aryl, aryloxy, heteroaryl, nitro, or cyano; or heterocyclyl]; and

R_3 is [halogen, hydroxy, mercapto, alkoxy, alkylthio, lower alkyl, or] $-NR_4R_5$; in which R_4 and R_5 independently are hydrogen or lower alkyl optionally substituted with one, two or three groups selected from hydroxy, lower alkoxy, halogen, amino, [mercapto, alkylthio, amido,] or carboxyl, [cyano, aryloxy, or acyl; or

aryl, arylalkyl, heteroaryl, heteroarylalkyl, or cycloalkyl where the ring portion of each is optionally substituted with one, two or three groups selected from lower alkyl, lower alkoxy, halogen, mercapto, alkylthiol, ethynyl, amino, amido, carboxyl, hydroxy, aryl, aryloxy, heteroaryl, nitro, or cyano;]

with the proviso that:

(1) when R_1 is benzyl or phenylethyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, R_2 is not [lower alkyl of C_{1-4}] methyl or ethyl; [and with the proviso that];

(2) R_1 cannot be cycloalkyl or endo-2-norbornyl when R_3 is halogen, hydroxy, or alkoxy;

R_2 and R_3 cannot both be lower alkyl;[and with the proviso that];

(3) when R_1' is optionally substituted alkyl, the optional alkyl substitution is not heteroaryl;

(4) when R_3 is 2-hydroxyethylamino and R_2 is methyl, R_1-X is not 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzyl-amino,

(5) when R_3 is 2-hydroxyethylamino and R_2 is isopropyl, R_1-X is not benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino;

(6) when R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, R_1 -X is not benzylamino and

(7) when R_3 is selected from the group consisting of 2-methyl-2-hydroxy propylamino and 2 dimethylaminoethylamino and R_2 is methyl, then R_1-X is not benzylamino;

or an acid addition salt[s] or [and] cationic salt[s] thereof.

49. The compound of claim 48, wherein X is -NH-.

50. (Once amended) The compound of claim 49, wherein R_1' is lower alkyl, substituted lower alkyl, aryl, substituted aryl, or heterocycle [, aralkyl, substituted aralkyl, hetaryl, or substituted hetaryl,].

Claims 51 and 52 are canceled from this application without prejudice.

53. (Twice amended) The compound of claim [52] 50, wherein R_4 and R_5 independently are hydrogen or lower alkyl substituted with hydroxy or amino.

54. (Once amended) The compound of claim 53, wherein R_4 [and] is hydrogen and R_5 [are] is [both] lower alkyl substituted with amino.

55. (Twice amended) The compound of claim 54, wherein [R_4 and] R_5 [are both] is 2-aminoethyl.

56. (Once amended) The compound of claim 55, wherein R_2 is lower alkyl.

57. (Once amended) The compound of claim 56, wherein R_2 is isopropyl.

58. (Twice amended) The compound of claim 57, wherein R_1' is 4-chlorobenzyl, 4-methoxybenzyl, pyridin-3-ylmethyl, or cyclopropylmethyl.

59. (Twice amended) The compound of claim [55] 53, wherein R_4 and R_5 are [both] independently hydrogen or lower alkyl substituted with hydroxy.

60. (Once amended) The compound of claim 59, wherein R_4 and R_5 are both 2-hydroxyethyl.

61. (Once amended) The compound of claim 60, wherein R_2 is isopropyl.

62. (Once amended) The compound of claim 61, wherein R_1' is 4-phenylbenzyl, 4-bromobenzyl, 4-bromophenyl, quinolin-3-yl, quinolin-5-yl, quinolin-6-yl, or quinolin-8-yl.

Claims 63 and 64 have been canceled from this application without prejudice.

65. (Twice amended) The compound of claim 49, wherein R_1' is lower alkyl, [substituted lower alkyl], cycloalkyl, or substituted cycloalkyl, [heterocyclyl, or substituted heterocyclyl,] R_2 is lower alkyl, and R_3 is $-NR_4R_5$, in which R_4 and R_5 independently are hydrogen or lower alkyl substituted with hydroxy or amino.

66. (Once amended) The compound of claim 65, wherein R_1' is lower alkyl of 1-8 carbon atoms and R_2 is isopropyl.

67. (Once amended) The compound of claim 65, wherein R_1' is cycloalkyl of 3-7 carbon atoms and R_2 is isopropyl.

68. (Twice amended) A method of inhibiting [treating a disease state in a mammal that is alleviable by treatment with] a cell cycle kinase characterized as CDK2 [inhibitor], comprising administering to a mammal in need thereof a therapeutically effective dose of a compound of claim 48.

Claim 69 has been canceled from the application without prejudice.

70. (Once amended) The method of claim [69] 68, wherein the inhibition of CDK-2 kinase treats a proliferative disease where pathogenesis involves [the disease state is characterized by] abnormal cell proliferation.

71. (Once amended) The method of claim 70, wherein the proliferative disease [state] is rheumatoid arthritis, lupus, diabetes, multiple sclerosis, cancer, restenosis, [graft-host disease] host-vs-graft disease, or gout.

72. (Once amended) The method of claim 70, wherein the proliferative disease [state] is cancer.

73. (Once amended) The method of claim 70, wherein the proliferative disease [state] is restenosis.

Claims 74 and 75 have been canceled.

76. (Once amended) A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 48.

77. The compound of claim 59, wherein R_4 is hydrogen and R_5 is 2-hydroxyethyl.

78. The compound of claim 77, wherein R_2 is isopropyl.

79. The compound of claim 78, wherein R_1' is 4-phenylbenzyl, 4-bromobenzyl, 4-bromophenyl, quinolin-3-yl, quinolin-5-yl, quinolin-6-yl, or quinolin-8-yl.